## REMARKS

The Office Action dated September 27, 2007 has been carefully reviewed and the foregoing amendments are made in response thereto. In view of the above amendments and following remarks, Applicants respectfully request reconsideration of this application and timely allowance of the pending claims.

The specification has been amended to delete paragraph [0002] on page 1 and correct the numbering of certain paragraphs from page 5 to page 31. Claims 40 and 50 have been amended to incorporate the features of the priming agent and the polymerizable agent as set forth in previously pending dependent claims 44-45 and 54-55, respectively. Specifically, amended claims 40 and 50 newly recite that the priming agent comprises a polysaccharide with at least one aldehyde group and at least one free radical polymerizable group, and the polymerizable agent comprises a biocompatible polymer having at least one free radical polymerizable group. Furthermore, step (b) in each of claims 40 and 50 has been amended to recite adding a radical photoinitiator and step (c) in each of claims 40 and 50 has been amended to recite a radical reaction. Dependent claims 44-45 and 54-55 have been amended to be consistent with the amended claims 40 and 50 from which they depend. In addition, claims 46 and 56 have been amended to replace "ultraviolet radiation" with "a source of electromagnetic radiation".

Support for the above amendments can be found throughout the disclosure as filed originally. Specific support for the above amendments can be found at least in the originally filed application as provided in the following table:

| *Claim Elements* | *Exemplary Support* |
|---|---|
| Claims 40 and 50:<br>(b) … a radical photoinitiator, … a biocompatible polymer … | Page 14, lines 23-24;<br>Page 15, lines 1-2 and lines 8-9;<br>Page 23, lines 19-28 (Example I);<br>Page 29, lines 4-9 (Example IV), and lines 25-31 (Example V);<br>Page 31, lines 22-25; and<br>Page 9, lines 11-30. |
| Claims 40 and 50:<br>(b) … by a radical reaction, … | Page 14, lines 23-24. |
| Claims 46 and 56:<br>…a source of electromagnetic radiation. | Page 3, lines 24-28;<br>Page 31, lines 26-28; and<br>Original claims 10 and 11 as filed. |

Thus, no prohibited new matter is introduced into the original disclosure. Upon entry of these amendments, claims 40 to 59 remain be pending.

**Summary of the Office Action**

1. The specification is objected to for alleged misnumbering of the paragraphs.

2. Claims 40 to 42, 44, 45, 47 to 52, 54, 55, and 57 to 59 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,458,889 to Trollsas et al. (hereinafter "Trollsas et al.").

3. Claims 43 and 53 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Trollsas et al. and further in view of Hai et al., Bioconjugate Chem., 2000, 11, 705-713 (hereinafter "Hai et al.").

4. Claims 46 and 56 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Trollsas et al. and further in view of Roberto Benson, Nuclear Instruments and Methods in Physics Research, 2002, B 191, 752-757 (hereinafter "Benson").

5. Claims 40 to 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 40 to 75 of copending Application No. 11/369,578.

6. Claims 40 to 42, 45 to 48, 50 to 52, and 55 to 58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 2, 9, 10, and 15 of copending Application No. 10/962,278 in view of Hai et al.

7. Claims 40 to 42, 45 to 48, 50 to 52, and 55 to 58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 4 to 7, 18, 22, and 23 of copending Application No. 11/637,516 in view of Hai et al.

8. Claims 40 to 42, 45 to 47, 49 to 52, and 55 to 58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 53, 63, 65, 77, and 86 of copending Application No. 10/681,753 in view of Hai et al.

**Specification**

The specification is objected to for alleged misnumbering of the paragraphs. Specifically, the Examiner asserts that the numbering of paragraphs [0025], [0026], and [0027] are duplicated on pages 4 and 5.

In response, Applicants have amended the specification to correct the numbering of the paragraphs. Since this amendment is only related to formal matters, no prohibitory new matter is introduced into the disclosure as originally filed.

**Rejections under 35 U.S.C. § 103(a)**

Claims 40 to 42, 44, 45, 47 to 52, 54, 55, and 57 to 59 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,458,889 to Trollsas et al. (hereinafter "Trollsas et al."). Claims 43 and 53 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Trollsas et al. in view of Hai et al., Bioconjugate Chem., 2000, 11, 705-713 (hereinafter "Hai et al."). Claims 46 and 56 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Trollsas et al. in view of Roberto Benson, Nuclear Instruments and Methods in Physics Research, 2002, B 191, 752-757 (hereinafter "Benson"). Specifically, the Examiner asserts that Trollsas et al., solely or in combination with Hai et al. or Benson, would have rendered the claimed invention obvious.

Applicants respectfully submit the claimed invention, as amended, is not rendered obvious by the references cited in the present Office Action because the cited references, solely or in combination, do not teach or suggest the claimed limitations of the present method, wherein, *inter alia*, the priming agent comprises a polysaccharide with at least one aldehyde group and at least one free radical polymerizable group; a polymerizable agent and a radical photoinitiator are added to the primed extracellular matrix; the polymerizable agent comprises a biocompatible polymer having at least one free radical polymerizable group; and reacting the primed extracellular matrix and polymerizable agent by a radical reaction to create a hydrogel covalently bound to the extracellular matrix.

Trollsas et al. disclose a composition containing at least three components crosslinkable with each other. However, the components and their crosslinking of Trollsas et al. are markedly different from the present invention because the Trollsas composition and its crosslinking are

based on polar reactions between nucleophiles and electrophiles, while the present composition and its crosslinking are based on free radical reactions.

Specifically, Trollsas et al. disclose that the composition is comprised of: (a) component A having m nucleophilic groups, wherein m≥2; (b) component B having n electrophilic groups wherein n≥2 and m+n>4; and (c) component C having at least one functional group which is either a nucleophilic group or an electrophilic group. (Column 2, line 55 to column 3, line 6; and column 10, line 40 to column 11, line 41). Trollsas et al. also teach that the nucelophilic and electrophilic groups are capable of reacting with each other to afford a crosslinked matrix when the components are admixed in an aqueous medium. (Column 2, line 55 to column 3, line 6; and column 10, line 40 to column 11, line 41). Thus, the crosslinking in Trollsas et al. is accomplished by polar reactions between nucleophiles and electrophiles.

In contrast, the present composition comprises a priming agent having an aldehyde group and at least one free radical polymerizable group, a radical photoinitiator, and a biocompatible polymer having at least one free radical polymerizable group, wherein the aldehyde group reacts with a functional group of the extracellular matrix, such as an amino group, to form a covalent bond, and the free radical polymerizable groups crosslink with each other via free radical reactions initiated by the radical photoinitiator. That is, the functional groups of the present composition include an aldehyde group for covalently bonding with the extracellular matrix and multiple free radical polymerizable groups for forming a crosslinked hydrogel. Furthermore, the crosslinking of different components in the present invention is through a radical reaction.

Radical reactions, as used in the present invention, and polar reactions, as used in Trollsas et al., are fundamentally two different types of chemical reaction. As discussed in Organic Chemistry, 3rd Edition, John McMurry, Brooks/Cole Publishing Company, 1992, Chapter 5, pages 142-149 (a copy is enclosed herewith), there are fundamentally two ways that a covalent bond can form: a bond can form in a homogenic way through a radical reaction, or in a heterogenic way through a polar reaction, i.e., a reaction between a nucleophile and an electrophile (Section 5.2 on pages 142-143, and Section 5.5 on page 148). More specifically, a radical reaction normally goes through three steps: an initiation step, a propagation step, and a termination step, wherein the radicals are electrically neutral, but highly reactive (Sections 5.3 and 5.4 on pages 143-145). On the other hand, a polar reaction forms a bond in an electronically

unsymmetrical way in which the electron-rich reagent, i.e., the nucleophile, donates a pair of electrons to the electron-poor reagent, i.e., the electrophile (Section 5.5 on pages 146-148). In other words, a radical reaction proceeds as a chain reaction once it is initiated, while a polar reaction is accomplished by one nucleophile reacting with one electrophile.

Since the Trollsas composition and its crosslinking method are based on polar reactions, which are fundamentally different from the radical reactions on which the present invention is based, the present invention, as amended, is markedly different from and non-obvious over the disclosure of Trollsas et al.

It is true that acrylate, methacrylate, and other examples of free radical polymerizable groups of the present invention are disclosed by Trollsas et al. as electrohilic groups. (Trollsas et al., column 12, lines 41-46). However, acrylate, methacrylate, and their derivatives, as used in the present invention, crosslink with other functional groups through free radical reactions, while the electrophilic groups of Trollsas et al. crosslink with other nucleophilic groups through polar reactions.

Even if, *arguendo*, acrylate, methacrylate, and their derivatives are considered as electrophilic groups in the present application, Trollsas et al. still fail to disclose or suggest the claimed limitations of the present method because Trollsas et al. require the presence of at least two nucleophilic groups (component A) in its composition, but there is at most one possible nucleophilic group in the present composition. Specifically, as discussed above, the Trollsas composition has at least three components, wherein component A has two or more nucleophilic groups ($m \geq 2$), component B has two or more electrophilic groups ($n \geq 2$), and component C has at least one nucleophilic group or electrophilic group. Thus, the Trollsas composition has at least two nucleophilic groups (component A). In contrast, the present composition contains a radical photoinitiator, a priming agent having an aldehyde group and at least one free radical polymerizable group, and a polymerizable agent having at least one free radical polymerizable group. Examples of the free radical polymerizable group include acrylate, methacrylate, and their derivatives. Trollsas et al. disclose that aldehyde, acrylate, and methacrylate are electrophilic groups. (Trollsas et al., column 12, lines 30-35, and column 13, Table 1) If, *arguendo*, acrylate, methacrylate, and their derivatives are considered as electrophilic groups, as alleged by the Examiner, the present composition would contain a radical photoinitiator, a

priming agent having at least two electrophilic groups, and a polymerizable group having at least one electrophilic group. Therefore, following the Examiner's reasoning, the only possible nucleophile in the composition is the free radical photoinitiator. It is known in the art that a radical photoinitiator upon activation can be either electrophilic, nucleophilic, or neutral. Thus, the present composition can at most contain one possible nucleophile, while the Trollsas composition comprises at least two nucleophilic groups (component A).

Therefore, Trollsas et al. do not teach or suggest the claimed limitations of the present invention.

The other applied references, namely, Hai et al. and Benson, fail to cure the defect of the principle reference, Trollsas et al. Specifically, Hai et al. disclose a method for preparing chondrotin-4-sulfate reagents and Benson reviews the use of radiation in biomaterials. Neither Hai et al. nor Benson teach or suggest reducing the number of nucleophilic groups of the Trollsas composition, let alone the use of a radical photoinitiator. Thus, combination of the cited references does not teach or suggest the present invention.

Furthermore, the 103(a) rejections also fail because there is no suggestion available in the cited references or otherwise of the record which can motivate one skilled in the art to modify the disclosed composition or crosslinking in such a way to arrive at the present invention. Trollsas et al. specifically emphasize that the crosslinkable composition contains at least three components wherein component A has at least two nucleophilic groups. Since the crosslinking in Trollsas et al. is accomplished by the polar reactions between nucleophilic groups and electropilic groups, it is necessary to have approximately equal number of nucleophilic groups and electropilic groups in the composition. Thus, it contravenes the basic principle of the Trollsas method to reduce the number of nucleophiles without proportionate reduction of electrophiles. In fact, Trollsas et al. suggest that if a higher degree of crosslinking is desired, more nucleophilic and electrophilic groups should be used in the composition. (Column 10, line 64 to column 11, line 5) That is, unlike the present invention wherein the composition has at most one possible nucleophile, Trollsas et al. suggest increasing the number of functional groups for desirable properties of the crosslinked composition. It is true that Benson disclose the use of radiation in biomaterials. However, as a review article, Benson merely summarizes the use of radiation in the biomaterial sciences in general terms and does not suggest the use of radiation in

the Trollsas composition to reduce the number of nucleophiles, let alone the use of radical photoinitiator.

The Examiner asserts that the use of radiation is suggested because Trollsas et al. state that it is preferred although not essential that reaction occur without need for ultraviolet or other radiation. Applicants respectfully submit that such a statement, when viewed in the context of the disclosure, conveys the preference of not using radiation. Particularly, Trollsas et al. actually teach away from using a radical photoinitiator:

> "X may be virtually any nucleophilic group, so long as reaction can occur with the electrophilic group Y ... The only limitation is a practical one, in that reaction ... should be fairly rapid and take place automatically upon admixture with an aqueous medium, without need for heat or potentially toxic or non-biodegradable reaction catalysts or other chemical reagents." (underline added, column 11, lines 43-54)

That is, the crosslinking reaction of Trollsas et al. takes place automatically upon admixture of the components and without catalysts or other chemical reagents. However, the crosslinking process of the present invention cannot take place automatically upon admixture of the components. It is necessarily initiated by a chemical reagent, namely, a radical photoinitiator, upon activation by radiation.

In the absence of specific teaching in Benson and the teaching away of Trollsas, Applicants respectfully submit that one skilled in the art would not be motivated to modify the Trollsas composition to reduce the number of nucleophiles and introduce a radical photoinitiator, as the present invention claims.

Therefore, the claimed invention is not rendered obvious by the cited references.

**Rejections under the Obviousness-type Double Patenting**

Claims 40 to 59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 40 to 75 of copending Application No. 11/369,578. Claims 40 to 42, 45 to 48, 50 to 52, and 55 to 58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 2, 9, 10, and 15 of copending Application No. 10/962,278 in view of Hai et al. Claims 40 to 42, 45 to 48, 50 to 52, and 55 to 58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 4 to 7, 18, 22, and 23 of

copending Application No. 11/637,516 in view of Hai et al. Claims 40 to 42, 45 to 47, 49 to 52, and 55 to 58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 53, 63, 65, 77, and 86 of copending Application No. 10/681,753 in view of Hai et al.

Applicants respectfully note the provisional obviousness-type double patenting rejections and will address these rejections when the Examiner indicates allowable subject matter in the present application.

**Conclusion**

In view of the foregoing, favorable reconsideration and allowance of the present application is respectfully solicited.

**Except** for issue fees payable under 37 C.F.R.§ 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R.§ 1.16 and § 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. § 1.136(a)(3).

Dated: January 28, 2008

Respectfully submitted,
**COOLEY GODWARD LLP**

By: _____
Yong Lu
Reg. No. 56,038

COOLEY GODWARD LLP
ATTN: Patent Group
777 6th Street, NW, Suite 1100
Washington, DC 20002
Tel: (202) 842-7800 or
(202) 842-7861
Fax: (202) 842-7899